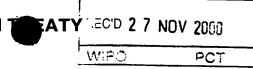
Joco

Applicant's or agent's file reference

PATENT COOPERATION



See Notification of Transmittal of International

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

110.008	1020	1	FOR FURTHER ACT	ACTION Preliminary Examination Report (Form PCT/IPEA/416)		Г/IPEA/416)	
Internation	al appl	ication No.	International filing date (day	/month/ye	ar)	Priority date (day/month/year)	
PCT/US	99/21	581	17/09/1999	17/09/1998			
International G01N33		ent Classification (IPC) or na	tional classification and IPC				
Applicant REGEN	rs ol	F THE UNIVERSITY O	F MINNESOTA et al.				
		ational preliminary exami smitted to the applicant a		epared by	/ this Inte	rnational Preliminary Exami	ning Authority
2. This	REPC	ORT consists of a total of	8 sheets, including this co	over shee	et.		
b (:	een a see R	mended and are the bas	is for this report and/or sh 07 of the Administrative Ins	eets con	aining re	n, claims and/or drawings who ctifications made before this e PCT).	
	J 4						
3. This r	eport	contains indications rela	ting to the following items:				
I	\boxtimes	Basis of the report					
II	\boxtimes	Priority					
III		Non-establishment of o	pinion with regard to nove	lty, inven	tive step	and industrial applicability	
IV		Lack of unity of invention	n				
V	⊠		nder Article 35(2) with regains suporting such statement		elty, inve	ntive step or industrial appli	cability;
VI	VI ☐ Certain documents cited						
VII	⋈	Certain defects in the in	ternational application				
VIII	. 🛛	Certain observations or	the international applicati	ion			
Date of sub	missio	on of the demand	D	ate of con	pletion of	this report	
13/04/20	00		2	3.11.2000			
	exam Euro D-80	g address of the international ining authority: opean Patent Office 0298 Munich	s	uthorized			THE PARTY OF THE P
<i>"</i>	Tel.	+49 89 2399 - 0 Tx: 523656	epmu d	,	_		\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\

Telephone No. +49 89 2399 8395



International application No. PCT/US99/21581

I. Basis of the report

1.	res _i the	ponse to an invitati		e sheets which have been furnished to the receiving Office in d to in this report as "originally filed" and are not annexed to ules 70.16 and 70.17).):
	1-2	0,22-30	as originally filed	
	21		with telefax of	10/04/2000
	Cla	ims, No.:		
٥	1-49	9	as originally filed	
	Dra	wings, sheets:		
	1/18	B-18/18	as originally filed	
2.	lang	guage in which the	international application was fil	d above were available or furnished to this Authority in the led, unless otherwise indicated under this item. uthority in the following language: , which is:
		the language of a	translation furnished for the pu	rposes of the international search (under Rule 23.1(b)).
		the language of pu	ublication of the international a	pplication (under Rule 48.3(b)).
		the language of a 55.2 and/or 55.3).		rposes of international preliminary examination (under Rule
3.				equence disclosed in the international application, the on the basis of the sequence listing:
		contained in the in	nternational application in writte	en form.
		filed together with	the international application in	computer readable form.
		furnished subsequ	ently to this Authority in writter	n form.
		furnished subsequ	ently to this Authority in comp	uter readable form.
			nt the subsequently furnished w pplication as filed has been fur	ritten sequence listing does not go beyond the disclosure in nished.
		The statement tha		omputer readable form is identical to the written sequence

4. The amendments have resulted in the cancellation of:

		the description,	pages:
		the claims,	Nos.:
		the drawings,	sheets:
5.		•	established as if (some of) the amendments had not been made, since they have been ond the disclosure as filed (Rule 70.2(c)):
		(Any replacement sh report.)	eet containing such amendments must be referred to under item 1 and annexed to this
6.	Add	itional observations, it	necessary:
II.	Pric	ority	
1.		This report has been prescribed time limit	established as if no priority had been claimed due to the failure to furnish within the the requested:
		☐ copy of the earlie	er application whose priority has been claimed.
		☐ translation of the	earlier application whose priority has been claimed.
2.	×	This report has been been found invalid.	established as if no priority had been claimed due to the fact that the priority claim has
	Thu date	· ·	his report, the international filing date indicated above is considered to be the relevant
3.		itional observations, if separate sheet	necessary:
V.			der Article 35(2) with regard to novelty, inventive step or industrial applicability; ns supporting such statement
1.	Stat	ement	
	Nov	elty (N)	Yes: Claims 1-24, 27-30, 48 No: Claims 25, 26, 31-47, 49
	Inve	ntive step (IS)	Yes: Claims none No: Claims 1-49
	Indu	ıs <u>trial applicabi</u> lity (IA)	Yes: Claims 1-49 No: Claims none

2. Citations and explanations see separate sheet

International application No. PCT/US99/21581

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Section II

The priority document does not disclose any device comprising one metabolically active biological material in general (only a few types of cells are mentioned, cf. p.7, l.8-12) and a non-porous latex-derived material. The priority date is therefore not valid for the subject-matter of the following-claims: totally as regards claims 1-6, 9-32, and 35-49; partially as regards claims 7 and 8.

The document D2 cited in the ISR is thus considered as prior art for the purpose of Art. 33.(2) and (3) PCT as regards the said claims (Rule 64(1) PCT).

Section V

Reference is made to the following documents:

D1: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, OLAV K. ET AL: 'A single use luciferase based biosensor using copolymerfilm immobilized viable E. coli HB101.' retrieved from STN XP002127579 & BOOK OF ABSTRACTS, 216TH ACS NATIONAL MEETING, BOSTON, AUGUST 23-27 (1998), BTEC-009 PUBLISHER: AMERICAN CHEMICAL SOCIETY, WASHINGTON, D. C.

DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, D2: US LYNGBERG, O. K. ET AL: 'A single-use luciferase-based mercury biosensor using Escherichia-coli-HB101 immobilized in a latex copolymer film' retrieved from STN Database accession no. 131:268025 XP002127580 & J. IND. MICROBIOL. BIOTECHNOL. (1999), 23(1), 668-676.

US-A-5 612 184 D3:

D4: WO 90 05910 A

D5: EP-A-0 318 452

1. D1 discloses a single use mercury biosensor consisting of two porous polymer layers, one of them comprising E. coli cells (cf. abstract). As the porosity usually varies within one polymer, there are at least two portions of different pore size.

EXAMINATION REPORT - SEPARATE SHEET

D1 is therefore prejudicial to the novelty of claims 25, 26, 31-41, 44 and 47 (Art. 33.2) PCT). Since the use of the device is mentioned, the method of claim 49 is also not novel over D1.

- D2 discloses a similar device further coated on polyester and specifies some other 2. technical features (cf. abstract). D2 is therefore prejudicial to the novelty of claims 25, 26, 31, 32, 35-41, 44, 47 and 49 (Art. 33.2) PCT)
- Any biological device containing an immobilized active biological material (e.g. 3. those of D1, D2, D4 and D5) is prejudicial to the novelty of the subject-matter of claims 25 and 26 (as the porosity usually varies within one polymer, there are at least two portions of different pore size).
- D3 is cited in the present application on p.2. This document discloses a device for 4. the detection of mercury (cf. columns 3 to 11, in particular c.8 and c.11, l.3) having all the features set out in claims 31 and 33-47 of the present application. D3 is therefore prejudicial to the novelty of the said claims (Art. 33(2) PCT).
- At this stage it should be noted that, even rendered novel, the subject-matter of 5. claims 32, 42, 43, 45 and 46 would not be considered as inventive since the combination of D1 (or D2) and D3, which would be seriously contemplated by the skilled person, would provide all technical features mentioned in these claims. The reasons therefor are the following: substrates capable of detecting a signal, especially light, are quite known in the art (see e.g. D3, c.8); the biosensor of D3 is capable of detecting a metal in a tissue (cf. c.11, first paragraph); D4 and D5 also disclose the immobilization of the biological material in one or more layers of a polymeric material.
- The device of claim 1 differs from those disclosed in D1 and D2 in that it 6. comprises a nonporous latex-derived material. The subject-matter of claims 1-24. the method of manufacturing such a device (claims 27-30) and the use of the said device (claim 48) are therefore novel (Art. 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as how to create a variety of structures within the device.



INTERNATIONAL PRELIMINARY International application No. PCT/US99/21581 **EXAMINATION REPORT - SEPARATE SHEET**

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) because the feature "nonporous latex-derived material" is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. A similar argumentation applies to the manufacturing and the use of such a device (claims 27 and 48).

In view of the cited prior art, dependent claims 2-24 and 28-30 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2, D4 and D5 are not mentioned in the description, nor are these documents identified therein.

Section VIII

- 1. The term biostructure used in the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of the concerned claims unclear (Article 6 PCT).
- 2. Although claims 1, 25 and 31 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subjectmatter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of



INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/US99/21581

the protection.

Hence, claims 1, 25 and 31 do not meet the requirements of Article 6 PCT. The same applies to claims 48 and 49 for similar reasons.

3. The statement which specifies that the non-porous latex-derived material is optional (cf. p.7, l.30-31) is not consistent with claim 1 and renders the latter unclear (Art. 6 PCT).

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Printed:05-05-2000

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Figure 10 discloses a device that includes a biostructure in the form of a cell-containing indicator coating coated on a fiber 100, composed of, for example, polyester, nylon, cellulose acetate, or an optical fiber. This fiber can be an optical fiber, for example. As shown in Figure 10A, the coated fiber 100 has an end-stop 101 and a penetrating end 103. The device is shown penetrating through a fish tail. Once a sufficient amount of time has lapsed for the immobilized cells of the cell-containing indicator to be in contact with the fish tissue, the coated fiber 100 is removed. As shown in Figure 10B, the coated fiber 100 is then placed in contact with a photosensitive film 104, which can be in a pouch or container, for example, having nutrients and buffer therein. After a sufficient incubation period, the mercury can be qualitatively detected by viewing a photographic image 105 of the thread on the photosensitive film 104.

Figure 11A shows a cross-section of a coated fiber 100, as shown in Figure 10. The coated fiber 100 includes a monofilament 106 coated with a biostructure 102. The biostructure 102 includes a cell-containing polymeric layer 107 and a polymeric overlayer 108. Figure 11B shows a cross-section of a coated fiber 110 that includes a multiple filament thread 116 with a biostructure 112. The biostructure 112 includes a cell-containing polymeric layer 117 and a polymeric overlayer 118. The coated fiber 110 may also include a polymeric precoat layer 119 between the multiple filament thread 116 and the cell-containing polymeric layer 107.

Figure 12 shows a device 120 in which cells are used that contain a plasmid with a mercury resistance promoter that activates a gene to produce a secreted protease or lipase. The cells are included in a biostructure 122. A popup indicator rod 121 is initially held in place by a protein or lipid based glue 123. The popup indicator rod 121 may be used either qualitatively or quantitatively, if it includes an indicator scale (not shown). The device also includes a spring 125 under tension that is attached to the pop-up indicator rod 121. In use, the device 120 is inserted into fish tissue. When mercury is detected by the cells in the biostructure 122 as it diffuses through a perforated housing 126 of device 120, the resulting protease or lipase degrades the glue 122 and releases the rod 121. As a result of the tension placed on the rod 121 by the spring 125, the rod moves up. By the design of the rod, the glue, and the glue holder the device could be made to be quantitative. Alternately, the pop-up indicator rod 121

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 110.00810201	FOR FURTHER see Notification (Form PCT/IS/	n of Transmittal of International Search Report V220) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 99/21581	17/09/1999	17/09/1998
Applicant		
REGENTS OF THE UNIVERSITY	OF MINNESOTA et al.	
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching A ansmitted to the International Bureau.	authority and is transmitted to the applicant
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in t	his report.
Basis of the report		
a. With regard to the language, the language in which it was filed, unl	international search was carried out on the ess otherwise indicated under this item.	basis of the international application in the
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of	of the international application furnished to this
was carried out on the basis of the	e sequence listing :	e international application, the international search
	onal application in written form.	orm
	rnational application in computer readable f this Authority in written form.	om.
	this Authority in computer readble form.	
the statement that the sul	osequently furnished written sequence listing is filed has been furnished.	g does not go beyond the disclosure in the
• • • • • • • • • • • • • • • • • • • •		π is identical to the written sequence listing has been
2. Certain claims were fou	nd unsearchable (See Box I).	
3. Unity of invention is lac	king (see Box II).	
4. With regard to the title ,		
The text is approved as su	bmitted by the applicant.	•
the text has been establis	shed by this Authority to read as follows:	
5 MGA valend to the chatrest		
5. With regard to the abstract,	ibmitted by the applicant.	
the text has been establis		ority as it appears in Box III. The applicant may, report, submit comments to this Authority.
6. The figure of the drawings to be pub		1
X as suggested by the appl	icant.	None of the figures.
because the applicant fail	ed to suggest a figure.	
because this figure better	characterizes the invention.	

INTER ATIONAL SEARCH REPORT



Α.	CLASSIF	ICATION OF SUBJEC	CT MATTER
	PC 7	G01N33/50	C1201/02

C12Q1/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ccc} \text{Minimum documentation searched} & \text{(classification system followed by classification symbols)} \\ IPC & 7 & G01N & C12Q \\ \end{array}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

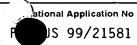
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X .	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, OLAV K. ET AL: "A single use luciferase based biosensor using copolymer-film immobilized viable E. coli HB101." retrieved from STN XP002127579 abstract & BOOK OF ABSTRACTS, 216TH ACS NATIONAL MEETING, BOSTON, AUGUST 23-27 (1998), BTEC-009 PUBLISHER: AMERICAN CHEMICAL SOCIETY, WASHINGTON, D. C.,	1-49

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "8" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2000	27/01/2000
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreno, C

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INTERMATIONAL SEARCH REPORT



		JS 99/21581
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Relevant to claim No.
Category °	Citation of document, with indication, where appropriate, of the relevant passages	nelevani to claim No.
P,X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, O. K. ET AL: "A single-use luciferase-based mercury biosensor using Escherichia coli HB101 immobilized in a latex copolymer film" retrieved from STN Database accession no. 131:268025 XP002127580 abstract & J. IND. MICROBIOL. BIOTECHNOL. (1999), 23(1), 668-676,	1-49
Α	PATENT ABSTRACTS OF JAPAN vol. 011, no. 369 (C-461), 2 December 1987 (1987-12-02) & JP 62 138502 A (TOKUYAMA SODA CO LTD), 22 June 1987 (1987-06-22) abstract	1,25-27, 31
Α	US 5 612 184 A (ROSSON REINHARDT A) 18 March 1997 (1997-03-18) cited in the application the whole document	1,25-27, 31
Α	WO 90 05910 A (I STAT CORP) 31 May 1990 (1990-05-31) the whole document	1,25-27, 31
Α	EP 0 318 452 A (MONSANTO EUROPE SA) 31 May 1989 (1989-05-31) abstract	1,25-27, 31
A	PATENT ABSTRACTS OF JAPAN vol. 012, no. 186 (C-500), 31 May 1988 (1988-05-31) & JP 62 294083 A (MITSUBISHI RAYON CO LTD;OTHERS: 01), 21 December 1987 (1987-12-21) abstract	1,25-27,

1

INTERNATIONAL SEARCH REPORT

ni n on pa

n on patent family members

ational	Application No
us	99/21581

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62138502 A	22-06-1987	JP 8026092 B	13-03-1996
US 5612184 A	18-03-1997	US 5571722 A AU 2422792 A CA 2114103 A EP 0597984 A JP 6509712 T WO 9303179 A	05-11-1996 02-03-1993 18-02-1993 25-05-1994 02-11-1994 18-02-1996
WO 9005910 A	31-05-1990	CA 2002848 A CA 2221178 A EP 0442969 A JP 4503249 T SG 45431 A US 5554339 A US 5200051 A US 5837446 A US 5837454 A US 5063081 A US 5212050 A US 5466575 A	14-05-1990 14-05-1990 28-08-1991 11-06-1992 16-01-1998 10-09-1996 06-04-1993 17-11-1998 17-11-1998 05-11-1991 18-05-1993 14-11-1995
EP 0318452 A	31-05-1989	AT 90383 T CA 1296060 A DE 3881653 A DE 3881653 T DK 600388 A ES 2058339 T US 4983510 A	15-06-1993 18-02-1992 15-07-1993 20-01-1994 30-04-1989 01-11-1994 08-01-1991
JP 62294083 A	21-12-1987	NONE	





From the INTERNATIONAL SEARCHING AUTHORITY

To:

MUETING, Ann M.

MUETING, RAASCH & GEBHARDT, P.A.

P.O. Box 581415 Minneapolis MN 55458-1415

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

UNITED STATES OF AMERICA	(PCT Rule 44.1)
	Date of mailing (day/month/year) 27/01/2000
Applicant's or agent's file reference 110.00810201	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.	International filing date
PCT/US 99/21581	(day/month/year) 17/09/1999
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA e	t al.
The applicant is hereby notified that the International Search Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claim	
When? The time limit for filing such amendments is normal International Search Report; however, for more de	ally 2 months from the date of transmittal of the tails, see the notes on the accompanying sheet.
Where? Directly to the International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41–22) 740.14.35	
For more detailed instructions, see the notes on the acco	mpanying sheet.
2. The applicant is hereby notified that no International Search Article 17(2)(a) to that effect is transmitted herewith.	n Report will be established and that the declaration under
3. With regard to the protest against payment of (an) addition	onal fee(s) under Rule 40.2, the applicant is notified that:
the protest together with the decision thereon has bee applicant's request to forward the texts of both the pro	n transmitted to the International Bureau together with the test and the decision thereon to the designated Offices.
no decision has been made yet on the protest; the app	olicant will be notified as soon as a decision is made.
4. Further action(s): The applicant is reminded of the following:	
Shortly after 18 months from the priority date, the international applicant wishes to avoid or postpone publication, a notice priority claim, must reach the International Bureau as provided completion of the technical preparations for international publications.	e of withdrawal of the international application, or of the in Rules 90 <i>bis</i> .1 and 90 <i>bis</i> .3, respectively, before the ation.
Within 19 months from the priority date, a demand for internation wishes to postpone the entry into the national phase until 30 mo	al preliminary examination must be filed if the applicant onths from the priority date (in some Offices even later).
Within 20 months from the priority date, the applicant must perform before all designated Offices which have not been elected in the priority date or could not be elected because they are not bound	e demand or in a later election within 19 months from the

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016

Authorized officer

Jaap Hurenkamp

FEB 0 3 2000

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international polication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

₩hen?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a damand for international preliminary examination has been its filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
 claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.





PCT

NOTICE INFORMING THE APPLICANT OF THE **COMMUNICATION OF THE INTERNATIONAL** APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

MUETING, Ann, M. Mueting, Raasch & Gebhardt, P.A. P.O. Box 581415 Minneapolis, MN 55458-1415

ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

23 March 2000 (23.03.00)

Applicant's or agent's file reference

110.00810201

IMPORTANT NOTICE

International application No. PCT/US99/21581

International filing date (day/month/year) 17 September 1999 (17.09.99) Priority date (day/month/year)

17 September 1998 (17.09.98)

Applicant

REGENTS OF THE UNIVERSITY OF MINNESOTA et al

Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice: AU.CN.JP.KP.KR.US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE, $\mathsf{GH}, \mathsf{GM}, \mathsf{HR}, \mathsf{HU}, \mathsf{ID}, \mathsf{IL}, \mathsf{IN}, \mathsf{IS}, \mathsf{KE}, \mathsf{KG}, \mathsf{KZ}, \mathsf{LC}, \mathsf{LK}, \mathsf{LR}, \mathsf{LS}, \mathsf{LT}, \mathsf{LU}, \mathsf{LV}, \mathsf{MD}, \mathsf{MG}, \mathsf{MK}, \mathsf{MN}, \mathsf{MW}, \mathsf{MX}, \mathsf{NO}, \mathsf{NZ}, \mathsf{OA}, \mathsf{MC}, \mathsf{MC},$

PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 23 March 2000 (23.03.00) under No. WO 00/16098

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Col mbettes 1211 Geneva 20, Switzerland

Authorized officer

J. Zahra MUETING AND RAASCH

Telephone No. (41-22) 338.83.38 Facsimile No. (41-22) 740.14.35



REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

TITLE OF INVENTION

REGENTS OF THE UNIVERSITY OF MINNESOTA

APPLICANT

100 Church Street Southeast Minneapolis, Minnesota 55455

United States of America

Box No. I

Box No. II

International Applica	tion No.		
International Filing I	Date		
	Jaic	** *	

Applicant's or agent's file reference 110.00810201 (if desired) (12 characters maximum) COMPOSITE DEVICES INCORPORATING BIOLOGICAL MATERIAL AND METHODS Name and address: (Family name followed by given name; for a legal entity, full official The address must include postal code and name of country. The country of the address indicated in this This person is also inventor. Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Telephone No. Facsimile No. Teleprinter No.

State (that is, country) of nationality: US	State (that is, country) of residence: US				
This person is applicant all designated all designated for the purposes of:	d States except the United States the States indicated in tates of America only the Supplemental Box				
Box No. III FURTHER APPLICANT(S) AND/OR (FURT	THER) INVENTOR(S)				
Name and address: (Family name followed by given name; for a legal er The address must include postal code and name of country. The country Box is the applicant's State (that is, country) of residence if no State of res	of the address indicated in this This person is:				
LYNGBERG, Olav K.	applicant only				
1022 Manvel Street	applicant and inventor				
Apartment 10	applicant and inventor				
St. Paul, Minnesota 55114 United States of America	inventor only (If this check-box is marked, do not fill in below.)				
State (that is, country) of nationality:	State (that is, country) of residence:				
US	US				
This person is applicant all designated all designate for the purposes of: States all designated the United St	d States except the United States the States indicated in tates of America only the Supplemental Box				
Further applicants and/or (further) inventors are indicated on	a continuation sheet.				
Box No. IV AGENT OR COMMON REPRESENTATIVE	; OR ADDRESS FOR CORRESPONDENCE				
The person identified below is hereby/has been appointed to act o of the applicant(s) before the competent International Authorities					
Name and address: (Family name followed by given name; for designation. The address must include postal of	a legal entity, full official Telephone No. (612)305-1217				
MUETING, Ann M.	Paris II. No				
MUETING, RAASCH & GEBHARDT, P.A.	Facsimile No. (612)305-1228				
P.O. Box 581415	(012)303-1228				
Minneapolis, Minnesota 55458-1415	Teleprinter No.				
United States of America	Totophilici 140.				
Address for correspondence: Mark this check-box where space above is used instead to indicate a special address to v	no agent or common representative is/has been appointed and the				
	LegalStar 1999, Form PCTREQ See Notes to the request form				
Form PCT/RO/101 (first sheet) (July 1998; reprint July 1999)	Legalical 1999, Foliar Circle Ser Notes to the request 1971				

Sheet	NΙα	2	

Continuation f Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)						
If none of the following sub-boxes is used, this sheet is not to be included in the request.						
Name and address: (Family name followed by given name; for a legal e The address must include postal code and name of country. The country Box is the applicant's State (that is, country) of residence if no State of reFLICKINGER, Michael C. 2226 Scudder Avenue St. Paul, Minnesota 55108 United States of America	y of the address indicated in this This person is:					
State (that is, country) of nationality: US	State (that is, country) of residence: US					
This person is applicant all designated for the purposes of:	d States except the United States the States indicated in tates of America only the Supplemental Box					
Name and address: (Family name followed by given name; for a legal e The address must include postal code and name of country. The country Box is the applicant's State (that is, country) of residence if no State of re SCRIVEN, L. E. (Edward) II 2044 Cedar Lake Parkway Minneapolis, Minnesota 55416 United States of America	of the address indicated in this This person is:					
State (that is, country) of nationality: US	State (that is, country) of residence: US					
This person is applicant all designated all designate for the purposes of:	d States except the United States the States indicated in tates of America only the Supplemental Box					
Name and address: (Family name followed by given name; for a legal e. The address must include postal code and name of country. The country Box is the applicant's State (that is, country) of residence if no State of re. ANDERSON, Ron 13645 Garrett Avenue Apple Valley, Minnesota 55124 United States of America	of the address indicated in this This person is:					
State (that is, country) of nationality: US	State (that is, country) of residence: US					
	d States except the United States the States indicated in tates of America only the Supplemental Box					
Name and address: (Family name followed by given name; for a legal en The address must include postal code and name of country. The country Box is the applicant's State (that is, country) of residence if no State of res	ntity, full official designation. of the address indicated in this This person is:					
State (that is, country) of nationality:	State (that is, country) of residence:					
This person is applicant ail designated all designated for the purposes of:	d States except the United States the States indicated in tates of America of America only the Supplemental Box					
Further applicants and/or (further) inventors are indicated on						

LengiStar 1999 Form PCTRFO

Box No.V DESIGNATION OF STEES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

National Patent (if other kind of protection or treatment desired, specify on dotted line):

X	AE	United Arab Emirates	X	1.R	Liberia
X	AL		\boxtimes		Lesotho
X	AM		\boxtimes		Lithuania
X	AT		\boxtimes		Luxembourg
		Austria	X		Latvia
	AU	Australia	X		
X	AZ	Azerbaijan			Republic of Moldova
X	BA	Bosnia and Herzegovina			Madagascar
X	BB	Barbados	\boxtimes	MK	The former Yugoslav Republic of Macedonia
\boxtimes	BG	Bulgaria	R-B		
\boxtimes	BR	Brazil	\boxtimes		Mongolia
\boxtimes	\mathbf{BY}	Belarus	X		' Malawi
\bowtie	CA	Canada	\boxtimes	MX	Mexico
\boxtimes	CH a	nd LI Switzerland and Liechtenstein	X	NO	Norway
\boxtimes	CN	China	X	NZ	New Zealand
X	CU	Cuba	\boxtimes	PL	Poland
\boxtimes	CZ	Czech Republic	\boxtimes	PT	Portugal
X	DE	Germany	\boxtimes	RO	Romania
X	DK	Denmark	X	RU	Russian Federation
X	EE	Estonia	X	SD	Sudan
X	ES	Spain	$\overline{\boxtimes}$	SE	Sweden
X	FI	Finland	X	SG	Singapore
X	GB	United Kingdom	X	SI	Slovenia
\boxtimes	GD	Grenada	X	SK	Slovakia
\boxtimes	GE	Georgia	X	SL	Sierra Leone
X	GH	Ghana	X	TJ	Tajikistan
	GM	Gambia	X		Turkmenistan
			\boxtimes		
	HR	Croatia			
X	HU	Hungary	X	TT	
X	ID	Indonesia	X		Ukraine
X	IL	Israel	X		Uganda
\boxtimes	IN	India	\boxtimes	US	United States of America
X	IS	Iceland			
\boxtimes	JP	Japan	\boxtimes		Uzbekistan
\boxtimes	KE	Kenya	X		Viet Nam
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\boxtimes	KR	Republic of Korea	Che	ck-bo	xes reserved for designating States which have become
$\overline{\boxtimes}$	KZ	Kazakhstan	part	y to th	e PCT after issuance of this sheet:
×	LC	Saint Lucia	\mathbf{X}	CR	Costa Rica
×	LK	Sri Lanka	X		Dominica

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Sheet	No	4

Box No. VI PRIORITY CLA						
Filing date	Number	Where earlier application is:				
of earlier application (day/month/year)	of earlier application	national application: country	regional application:* regional Office	international application: receiving Office		
item (1) 17 September 1998 (17.09.98)	60/100,914	us				
item (2)						
item (3)						
of the earlier application	n(s) (only if the earlier of international application in RIPO application, it is mandator	transmit to the International application was filed with is the receiving Office) iden by to indicate in the Supplemental and (Rule 4.10(b)(ii)). See Supplemental controls of the supplementa	the Office which for the tified above as item(s): Bas at least one country part	(1)		
Box No. VII INTERNATION	ONAL SEARCHING AU	THORITY				
Choice of International Searching (if two or more International Se competent to carry out the international Authority chosen; the two-letter coa	earching Authorities are ional search, indicate the	Request to use results of ear search has been carried out by or Date (day/month/year)	r requested from the Internation			
ISA/EP						
Box No. VIII CHECK LIST	T: LANGUAGE OF FIL	ING				
This international application of the following number of sheet.		nal application is accompa lation sheet	nied by the item(s) mark	ced below:		
request :	4 2. separate	signed power of attorney				
description (excluding)		general power of attorney; re	eference number, if any	: ·		
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Figure of the drawings which should accompany the abstract:	1 La	nguage of filing of the ernational application:	e Eng	lish		
Box No. IX SIGNATURE	OF APPLICANT OR A	GENT	•	,		
Next to each signature, indicate obvious from reading the reques	e the name of the person st).	signing and the capacity in	n which the person sign	s (if such capacity is not		
SANDBERG, Victoria A. Occidentalise						
,						
For receiving Office use only 2. Drawings:						
international application: 3. Corrected date of actual receipt due to later but received:						
timely received papers or drawings completing the purported international application:						
4. Date of timely receipt of the required corrections under PCT Article 11(2):						
5. International Searching Auth (if two or more are competer			l of search copy delayed n fee is paid			

Form PCT/RO/101 (last sheet) (July 1998; reprint July 1999)

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See Notes to the request form